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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,073	06/27/2003	Michael D. Schneider	HO-P02514US2	1078

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/609,073	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-23 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-23 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/22/04 & 5/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 11-23 and 27 are presented for examination.

Acknowledgement is made of Applicant's claims for priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 60/392,744, filed June 28, 2002, and 60/426,883, filed November 15, 2002. Applicant's Information Disclosure Statements (IDS) filed January 22, 2004 (two pages total) and May 20, 2005 (one page total) have each been received and entered into the application. As reflected by the attached, completed copies of form PTO/SB/08 (three pages total), the Examiner has considered the cited references.

Applicant's response filed September 28, 2005 to the restriction requirement dated August 30, 2005 has also been received and entered into the application. Accordingly, claims 1-10, 24-26 and 28-35 have been cancelled.

Requirement for Restriction/Election

Applicant's election **without traverse** of the invention of Group II (claims 11-23 and 27), drawn to method of modulating myocyte enlargement in a subject at risk for cardiac hypertrophy or a method of modulating cardiac hypertrophy comprising the administration of an effective amount of a composition to modulate cyclin dependent kinase 9 activity or a method of treating a subject at risk for ventricular dysfunction associated with cardiac hypertrophy comprising the administration of an effective amount of a composition to modulate cyclin dependent kinase 9 activity, and cancellation of claims 1-10, 24-26 and 28-35 in the reply filed September 28, 2005 is acknowledged by the Examiner.

Insofar as Applicant has canceled the claims directed to the other groups of invention, the restriction requirement set forth in the previous Office Action dated August 30, 2005 is **moot** and is, therefore, **withdrawn**.

The pending claims corresponding to the elected subject matter are 11-23 and 27 and such claims are herein acted on the merits.

Objection to the Specification

The disclosure is objected to because the word "systolic" at page 7, line 4 of paragraph [0030] is misspelled. Appropriate correction is required.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

I Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claim 22 recites the limitation "The method of claim 21, wherein the Gq inhibitor is selected from the group consisting of..." at lines 1-2 of the claim. There is insufficient antecedent basis for the limitation "the Gq inhibitor..." in claim 22, since any reference to such an inhibitor in the claims from which it depends (i.e., claim 18 or claim 21) is noticeably absent. It is unclear how Applicant intends claim 22 to limit the presently claimed subject matter. As a

result, the claim fails to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and is properly rejected for rendering the scope of the claim indefinite.

For the purposes of examination and the application of prior art, claim 22 will be interpreted to further limit the subject matter of claim 20.

II Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, Applicant has failed to define the compounds intended to be within the scope of claim 23, wherein the claim recites, "...wherein the composition comprises a compound that upregulates the levels of 7SK snRNA." (See lines 1-2 of claim 23)

The MPEP sets forth the following at §2173:

> "The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (See MPEP §2173).

In the present specification at page 20, paragraph [0085], Applicant has set forth:

> "Yet further, other compounds can be used to modulate Cdk 9 activity, for example, a compound that upregulates the levels of 7SK snRNA. Upregulation of the levels of 7SK snRNA can provide sufficient amounts of 7SK snRNA to ensure that 7SK snRNA stays associated with the cyclin T/Cdk9 complex."

Such disclosure, however, does not render the claims definite. Words and phrases in the claims must be given their "plain meaning" as understood by one having ordinary skill in the art unless defined by Applicant in the specification with "reasonable clarity, deliberateness and

precision" (MPEP §2111.01). Here, Applicant has not adequately delineated the compounds that fall within the scope of the phrase "a compound that upregulates the levels of 7SK snRNA" and, thus, fails to meet the requirement for reasonable clarity, deliberateness or precision. Thus, the identity of those compounds that are included or excluded by the phrase "compound that upregulates the levels of 7SK snRNA" is open to subjective interpretation and would not reasonably apprise the public of what subject matter would constitute infringement of the present claims. Such is inconsistent with the tenor and express requirements of 35 U.S.C. §112, second paragraph and, thus, the claim is properly rejected.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11, 14-15, 18-22 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Grant et al. (U.S. Patent No. 6,201,165, 2001; cited by Applicant).

Grant et al. teach method for treating cardiac hypertrophy-induced dysfunction [i.e., cardiac hypertrophy, compound or dilated or decompensated cardiac hypertrophy, or concentric or eccentric enlarged ventricular mass (considered to meet Applicant's limitation of "ventricular dysfunction associated with cardiac hypertrophy as recited in claim 27); see Grant et al., col.12, lines 58-66 and present claims 11, 15 and 27], comprising administering to an individual in need

of such treatment a composition comprising a substance which modulates active levels of at least one product of a gene expressed in response to a hypertrophic signal (col.10, lines 52-57), such as calcineurin inhibitors (col.29, lines 11-14), endothelin receptor antagonists (col.30, lines 6-7), ACE inhibitors, including ACCUPRIL, ALTACE, CAPOTEN, LOTENSIN, MONOPRIL, PRINIVIL, VASOTEC or ZESTRIL (col.30, lines 7-10) or known angiotensin II receptor antagonists (col.3, lines 37-41), by administering an effective amount necessary to achieve amelioration or palliation of cardiac hypertrophy or any one of the other conditions (col.29, lines 7-10; considered to meet Applicant's limitation of an "effective amount" as recited in present claims 11, 15 and 27; see also present claims 11, 14-15, 18-22 and 27). Grant et al. further teach that the individual in need thereof may also be individuals who have a genetic predisposition to developing cardiac hypertrophy (considered to meet Applicant's limitation of "in a subject at risk for cardiac hypertrophy" as recited in present claim 11; col.32, lines 11-24).

Applicant has defined "compounds that modulate cdk9 activity by prohibiting the dissociation of 7SK snRNA from cyclin T/cdk9 complex" (see present claims 11, 14, 15, 18 and 27) at paragraph [0084] bridging pages 19-20 of the present specification as inhibitors of Gq and calcineurin, including, but not limited to, angiotensin II antagonists, ACE inhibitors or endothelin inhibitors. Grant et al. directly anticipates such a limitation as discussed above in the preceding paragraph, citing directly to the reference.

The limitations of "...an effective amount of a composition to modulate cyclin dependent kinase 9 (cdk9) activity, wherein the effective amount modulates myocyte enlargement" (see present claim 11), "...an effective amount of a composition to modulate cyclin dependent kinase 9 (cdk9) activity, wherein the effective amount modulates hypertrophic growth" (see present

claim 15) or "...an effective amount of a composition to modulate cyclin dependent kinase 9 (cdk9) activity..." (see present claim 27) have each been considered, but amount to no more than a recitation of the function of the composition and fail to impart any material or physical property to the composition that is not already present in the composition of the prior art of Grant et al.

While it has been noted that Grant et al. is silent as to the function of angiotensin II antagonists, ACE inhibitors or endothelin inhibitors in modulating myocyte enlargement, such an omission by the reference is not considered to be a patentable distinction between the present claims and the prior art of Grant et al. because such a limitation is merely a recitation of the end result of the therapeutic action of the drug. Because Grant et al. teaches the presently claimed method steps of administering an effective amount of an angiotensin II receptor antagonist, a calcineurin inhibitor, an ACE inhibitor or an endothelin receptor antagonist to an identical host as presently claimed (i.e., a subject with a genetic predisposition to developing cardiac hypertrophy), it is deemed that the modulation of myocyte enlargement would have been the necessary therapeutic end result of administering such compounds to a subject with a genetic predisposition to developing cardiac hypertrophy, whether recognized by the patentee or not.

It is further noted that the very administration of an identical compound in an identical host in substantially identical amounts cannot exert mutually exclusive properties, since a chemical compound and its properties are inseparable and would be expected to have the same therapeutic end result in the same host. Thus, the present claims are merely drawn to a new "function" or new property of a composition identical to that disclosed by the prior art of Grant et al., not a new "use". The recitation of a new "use" of a compound, wherein the new "use"

amounts to no more than a function or new property of an old compound known in the art, is properly anticipated. See MPEP §2112.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-13, 15-17 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abdellatif et al. ("A Ras-Dependent Pathway Regulates RNA Polymerase II Phosphorylation in Cardiac Myocytes: Implications for Cardiac Hypertrophy", *Molecular and Cellular Biology*, 1998; cited by Applicant) in view of Chao et al. ("Flavopiridol Inhibits P-TEFb and Blocks HIV-1 Replication", *Journal of Biological Chemistry*, 2000; cited by Applicant).

Abdellatif et al. teach that cardiac hypertrophy is accompanied by enhanced activity of RNA polymerase II, which regulates synthesis of mRNA, which contributes to the regulation of overall protein synthesis, which, in turn, increases the total protein per cell, a distinct characteristic of cardiac hypertrophy. Abdellatif et al. provide experimental evidence showing that Ras-dependent phosphorylation of RNA polymerase II is a potential mechanism for the total protein increase per cell that is characteristic of cardiac hypertrophy (page 6730, paragraph 1, column 1; see present claims 11 and 15).

Chao et al. teach flavopiridol, a cyclin-dependent kinase (cdk) inhibitor that potently inhibited transcription by RNA polymerase II in vitro by blocking the phosphorylation at the carboxy-terminal domain of the large subunit of RNA polymerase II by P-TEFb, which is composed of cdk9 and cyclin T1 [see abstract at page 28345, for example; see present claims 12-13, 16-17 and 23; (such a characteristic is considered to meet Applicant's limitation that the compound modulates, by inhibition, cdk9 activity, since flavopiridol inhibits RNA polymerase II by inhibiting phosphorylation by P-TEFb, which necessarily inhibits cdk9 since cdk9 is a component of P-TEFb].

Claim 23 is properly included in the present rejection because Applicant has failed to define the particular agents intended to be within the scope of claim 23, "...wherein the composition comprises a compound that upregulates the levels of 7SK snRNA". Absent any factual evidence to the contrary, there is no reason to doubt that the compound flavopiridol does not have the same upregulation properties of 7SK snRNA as that of the compounds within the scope of present claim 23 (see above under "Claim Rejection-35 U.S.C. 112, Second Paragraph").

The difference between the Abdellatif et al. reference and the presently claimed subject matter lie in that the reference does not teach the administration of flavopiridol for the modulation of myocyte enlargement, cardiac hypertrophy or ventricular dysfunction associated with cardiac hypertrophy. However, the difference between the presently claimed subject matter and the prior art of Abdellatif et al. and Chao et al. are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time of the invention.

When the teachings of Abdellatif et al. are considered in view of Chao et al., it is obvious that one of ordinary skill in the art would have been motivated to use flavopiridol for the modulation of myocyte enlargement, cardiac hypertrophy or ventricular dysfunction associated with cardiac hypertrophy because the prior art recognized the function of enhanced RNA polymerase II in increasing the total protein content in hypertrophic cardiac cells, which directly results in an increase in cell volume and mass (see Abdellatif et al., page 6734, paragraph 2 at column 2). To the skilled artisan, such a teaching would have reasonably suggested that the inhibition of RNA polymerase II would have beneficial effects in reducing the excess transcription occurring in the hypertrophic cardiac cells, thus, modulating (i.e., reducing) the enlargement of the cells by decreasing the amount of total protein. The acknowledgement that flavopiridol was capable of inhibiting RNA polymerase II transcription activity by blocking P-TEFb phosphorylation of RNA polymerase II would have led the skilled artisan to recognize that such a compound would have been reasonably expected to exert an inhibitory action not only on RNA polymerase II, but also on the production of total protein resulting from the transcription that occurs via RNA polymerase II. Thus, an inhibitory action on cellular enlargement resulting

from the increased total cellular protein that occurs in cardiac hypertrophy would necessarily occur.

While it is acknowledged that the references do not explicitly teach the treatment of ventricular dysfunction associated with cardiac hypertrophy, it is noted that the amelioration or the reduction in the incidence of cellular enlargement as occurs with cardiac hypertrophy would have reasonably been expected to further ameliorate the dysfunction or disorders (i.e., ventricular dysfunction) that would necessarily have resulted from said cellular enlargement and such would have been plainly obvious to the skilled artisan.

Furthermore, it is noted that the administration of an effective amount of such an agent to a subject in need thereof would have been well within the knowledge generally available to one of ordinary skill in the art and the determination of such effective amounts would have been a matter within the purview of the skilled artisan. Such a determination would have been made in accordance with a variety of factors, such as the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosages that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific dosage amounts are not seen to be inconsistent with the dosages that would have been determined by the skilled artisan.

Notwithstanding that Applicant may have discovered a different, underlying mechanism of action of the compound flavopiridol that is not explicitly recognized in the prior art that led

Applicant to employ flavopiridol in the treatment of cardiac hypertrophy, such does not change the fact that the prior art would have rendered the use of such an agent for the treatment of such a disease (or related conditions thereto) obvious to the skilled artisan motivated by a different reason for attempting such a combination. The fact that Applicant has recognized another advantage that flows naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise have been obvious.

Double Patenting

Statutory-Type (35 U.S.C. §101)

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 11-23 and 27 are provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 11-23 and 27 of copending United States Patent Application No. 10/665,336. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

Rejection of claims 11-23 and 27 is deemed proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-6:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

October 25, 2005

DWAYNE JONES
PRIMARY EXAMINER